Selective Inhibition of Matrix Metalloproteinase-9 Attenuates Traumatic Brain Injury-Mediated Blood-Brain Barrier Disruption in a Novel Dynamic *in vitro* Model

Traumatic Brain Injuries

- Physical injury from an **external force** that causes impairment
- Inflammatory responses to primary injury amplify **structural damage**
- **No reparative treatment–** current methods have poor outcomes

Blood-Brain Barrier

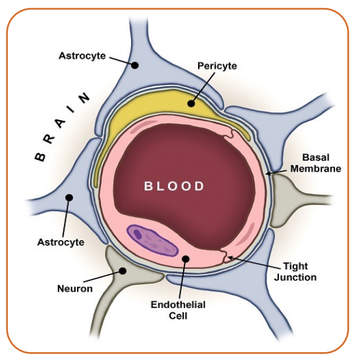


Figure 1. Cross Section of the BBB (Campbell, n.d.)

BBB Structure

- Endothelial cells, astrocytes, and pericytes
- Cells have special characteristics that create **restrictive permeability**
- Tight junctions enforce structural integrity
- Matrix metalloproteinases maintain function

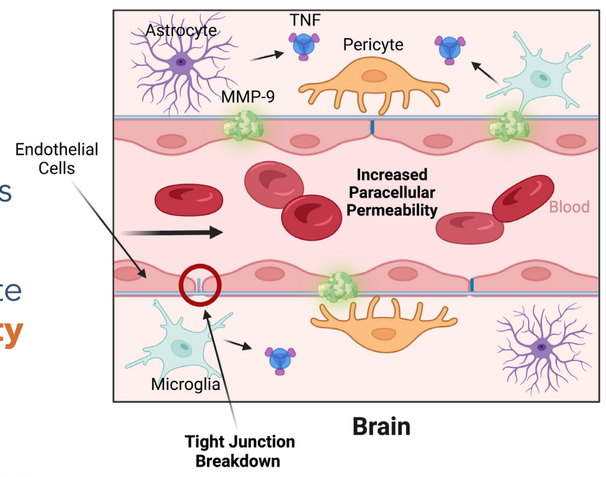


Figure 2. TBI activates an inflammatory response (Created by author with BioRender).

Novel Dynamic Model

Model Overview

- **Tri-culture** of human endothelial cells, astrocytes, and pericytes
- **Perfused** with continuously circulating media
- Mimics **physiological conditions** on the vascular and interstitial side
- **Real-time** and continuous measurements of barrier integrity, including TEER, hydraulic conductivity, and permeability assays
- Cells are **continuously accessible** for treatment variations

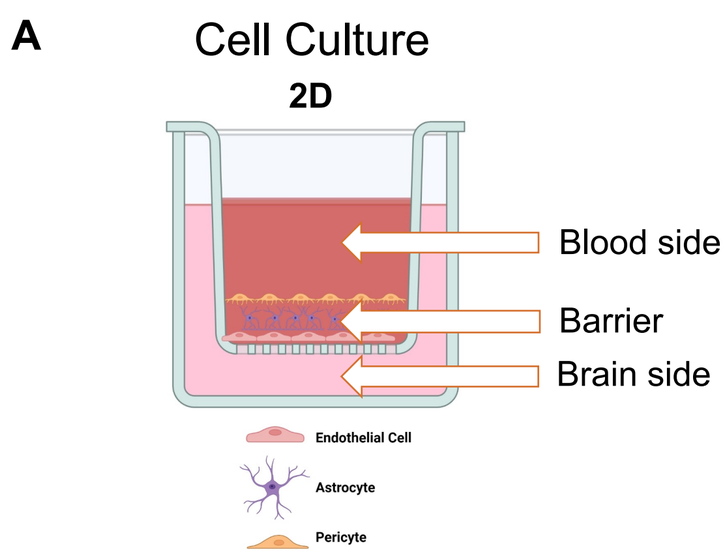
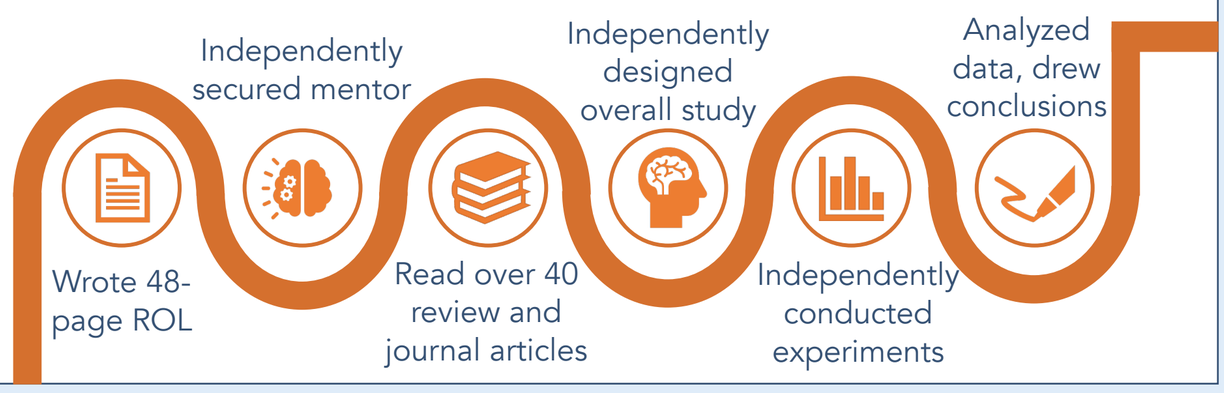
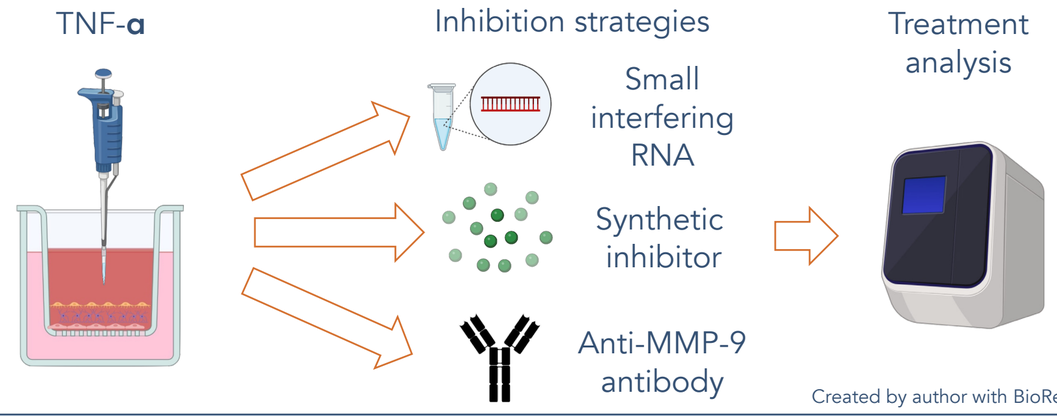


Figure 3. **(A)** Barrier tri-culture in Transwell. **(B)** Schematic representation of platform (Bolden et al., 2023).

My Role



Methods



Results: Platform Metrics

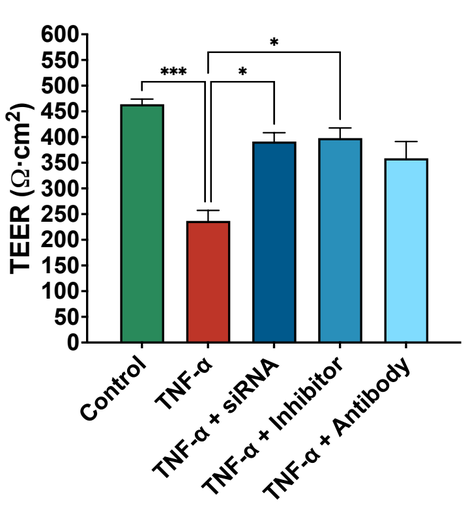


Figure 4. Barrier ion resistance post-treatment (One-way ANOVA, N=6).

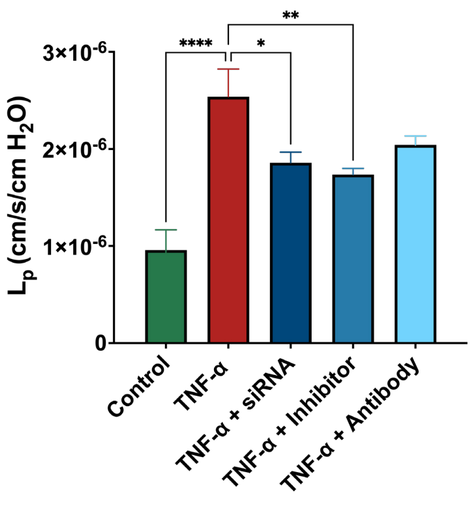


Figure 5. Fluid accumulation rate (One-way ANOVA, N=6).

Results: Post-lysis Analysis

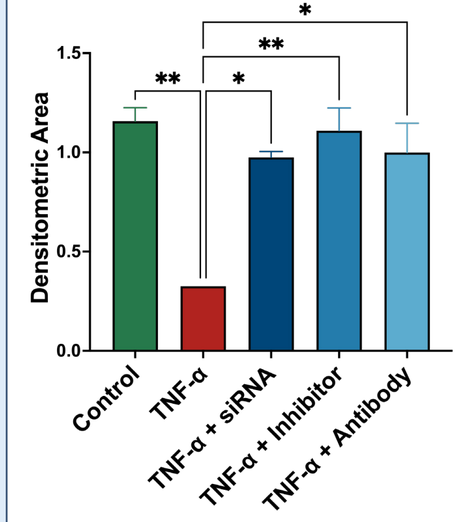


Figure 6. Claudin-5 expression (One-way ANOVA, N=2).

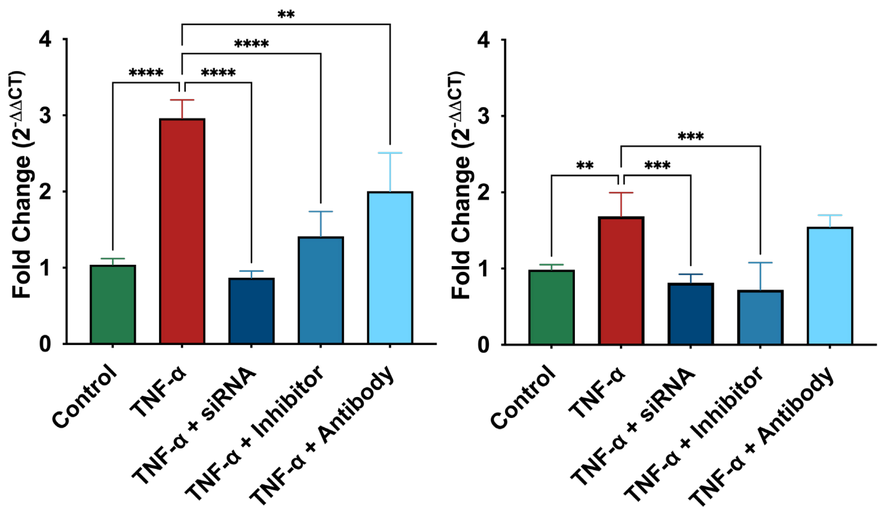


Figure 7. MMP gene amplification/knockdown (A) MMP-9. (B) MMP-2 (One-way ANOVA, N=2).

Discussion

MMP-9 inhibition → Restored barrier function → Increased Claudin-5

Antibody	siRNA and inhibitor
Only knocked-down MMP-9 expression	Knocked-down MMP-9 and **MMP-2** expression
Least effective	Significantly effective

MMP-2 also plays a role in **TBI-induced** BBB hyperpermeability

Future Directions

- Validate findings with **additional trials** in **expanded model**
- Model **other** barrier-modifying **diseases**
- Treatments **preventing** MMP-9 and MMP-2 **upregulation**
- Target MMPs in **diseases beyond TBI**